II. Preliminary Remarks

A. Preliminary Comments With Respect to Advisory Office Action

On July 31, 2007, an advisory office action was mailed for the above identified patent application in which the Examiner informs Applicants that amendments to the pending claims filed by Applicants on July 10, 2007 were not entered because "they raise new issues that would require further consideration and/or search."

In response, Applicants request herewith continued examination for the above-identified patent application and resubmit the amendment to the claims and patentability arguments filed on July 10, 2007.

B. Interview Summary

The Applicants thank the Examiner for the courtesy and diligence shown during the interview of May 30, 2007, during which the substance of the rejections were discussed.

C. IDS

Regarding the IDS filed on October 20, 2004, which included the Submission of Protective Order Materials Under MPEP § 724; cited references; Petition to Expunge Under 37 C.F.R. § 1.59(b); Supplemental Information Disclosure Statement; PTO Form SB/08A; and stamped-returned postcard, the applicants submit herewith a copy of the listed documents as filed on October 20, 2004. These documents were also provided with Applicants' response filed on July 10, 2007.

D. Amendment Support

The claims have been amended to replace the phrase "dAb fragment" with the phrase "an antibody heavy chain variable domain." Support for this amendment is found, for example, on page 3, lines 8-9, which describes molecules which function to bind antigens including "...the dAb fragment (Ward, E. S., et al., *Nature*, 341, 544-546 (1989) which consists of a VH domain..." Example 3 of the specification also describes the insertion of an antilysozyme antibody heavy chain variable domain into a bacteriophage. Figure 1 also depicts an antibody heavy chain variable domain (also referred to in the figure as dAb).

E. Patentability Arguments

1. The Rejection Under 35 U.S.C. § 102(e) Should Be Withdrawn

The Examiner has maintained the rejection of the claims under 35 U.S.C. § 102(e) as allegedly being anticipated by Dower. The applicants respectfully traverse the rejection and request reconsideration in view of the following.

The pending claims of the instant application as presently amended require that the binding domain of the binding molecule consists of an antibody heavy chain variable domain. The claims of Dower are directed to screening a DNA library for nucleotide sequences which encode "an antibody Fab fragment comprising first and second polypeptide chains, one chain comprising a light chain variable region and another chain comprising a heavy chain variable region." Clearly, as was well known in the art and as described in Dower, Fab molecules are not the same as antibody heavy chain variable domain. Example 1 of Dower is similarly directed to display of Fab molecules, in which one polypeptide chain composed of VH and CH domains is presented as a fusion with bacteriophage gene III protein and displayed with an associated second polypeptide composed of VL and CL domains to provide a binding domain formed by the VH and VL domains together.

Dower is concerned with provision of multichain proteins in general and Fab molecules in particular, as reflected throughout columns 1-12. Each mention of VH and VL chains throughout Dower is for the identification and cloning, with it being explicitly stated that it is "the binding fragments (Fv) or Fab encoded thereby" that are to be employed, i.e., multichain proteins in which VH and VL domains associate to form a binding domain. *See* for example, Dower, column 3, lines 28-41. The cloning of VH and/or VL domains is further elaborated at Dower, column 4, lines 51-64 where the use of separate cloning vectors for antibody light and heavy chain sequences is suggested from which a combinatorial library is constructed to bring together VH and VL domain sequences in pairs associated to form binding domains. Moreover, in relation to column 4, Applicants direct the Examiner's attention to the fact that this is in relation to use of bacteriophage lambda, which is a lytic phage assembled intracellularly and not a filamentous bacteriophage as required by the instant claims. Furthermore, the reference is explicitly to expression, not display and citation is given to Huse *et al.*, Science 246:1275-1281 (1989) and Short *et al.*, Nucleic Acids Res. 16:7583 (1988), both of which are concerned with expression from lambda vectors and not bacteriophage display. Thus, Dower relates to display

of multichain proteins, mostly Fab, with a suggestion of Fv, and not antibody heavy chain variable domains as required by the present claims. Accordingly, Applicants respectfully submit that claims 9 and 15-17 are not properly anticipated by Dower and hereby request withdrawal of the rejections under U.S.C. §102(e).

2. The Rejection of Claim 9 Under 35 U.S.C. §103 Should be Withdrawn

The Examiner has also maintained the rejections under 35 U.S.C. §103(a) as allegedly unpatentable over WO 90/02809 (hereinafter "Ladner and Guterman") and WO 88/06630 (hereinafter "Ladner *et al.*"). The Examiner characterizes Ladner and Guterman as teaching display of binding domains, encoded by nucleic acid sequences, on the surface of filamentous bacteriophage and screening via binding to targets. The Examiner further characterizes Ladner and Guterman as failing to expressly convey the expression of antibody fragments on the surface of filamentous phage. The Examiner characterizes Ladner *et al.* as teaching methods of displaying SCADs or single-chain antibodies on the surface of Lambda phage and screening against antigens. The Examiner alleges variously throughout the file history that it would have been obvious to one of ordinary skill in the art at the time the invention was made "to alter the methods of screening filamentous phage displaying proteins of Ladner and Guterman with the SCADs or antibody fragments of Ladner et al."

The Examiner's rejection of claim 9 under 35 U.S.C. §103(a) relies on the Examiner's belief that Ladner *et al.* discloses use of molecules that are an essential component of the present claims, i.e. that Ladner *et al.*'s "SCADs" equate to VH domains of antibodies. In fact, the "SCADs" of Ladner *et al.* are more commonly known as scFv or single-chain Fv molecules which consist of a VH domain and a VL domain joined by a peptide linker so that the binding domain is composed of the VH and VL domain. As presently amended, the claims recite *"an antibody heavy chain variable domain"* as the only binding domain present on the surface of phage. In other words, the present invention is concerned with <u>different molecules</u> from those of Ladner *et al.* Further, Lambda phage disclosed in Ladner is not a filamentous phage as is required by the present claim.

The nature of the SCAD's can be understood from the material presented in Ladner *et al.* as the source of the term, i.e., copending U.S. Patent Application No. 10/902,970. U.S. Patent Application 10/902,970 issued as U.S. patent 4,704,692 (hereinafter the "'692 patent"). The

'692 patent teaches a method for "generating single chain structures from two-chain aggregate structures, wherein the single chain will retain the three-dimensional folding of the separate natural aggregate of two polypeptides chains." See '692 patent, column 2, lines 31-35. One of ordinary skill in the art would understand that the '692 patent teaches the creation, in a single polypeptide chain, of a replica of an Fv molecule, which is a two-chain molecule consisting of a VH domain and a VL domain associating to form a single binding domain. *See* also, e.g., '692 patent, figures 6B and 7.

Accordingly, the combination of Ladner and Guterman with Ladner *et al.* does not teach or suggest the display of an antibody heavy chain variable domain on the surface of a filamentous bacteriophage, and therefore cannot properly render claim 9 obvious. In view thereof Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

III. Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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